Prostate Cancer Working Group Report

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The incidence of prostate cancer, while still lower than in Western nations, is increasing rapidly in Asian countries due to a more westernized lifestyle. Prostate cancer mortality is declining in the USA, where most prostate cancers are diagnosed in the early stage. In contrast, the mortality rates of prostate cancer in Asian countries are expected to continue to increase, because the percentage of advanced-stage prostate cancers remains high. Therefore, early detection by prostate-specific antigen screening and a comprehensive strategy for cancer prevention are essential for Asian people. The exposure rate of prostate-specific antigen screening is very low in Asian countries. Increased prostate-specific antigen screening may reduce the mortality rate. The stances regarding population screening differ among countries. Urological associations should promote population screening. Reliable data from Asian countries are needed. The prostate cancer incidence is low in Asian countries, perhaps due to high soy consumption. Isoflavones may prevent prostate cancer in Asian countries, but that is not yet clear. A large, multinational study in Asia is needed to clarify whether or not isoflavone consumption shows efficacy in preventing prostate cancer. Clinical data suggest that hormonal therapy is more effective in Asians than in Westerners. Clinical guidelines should consider including hormonal therapy as one of the options for the treatment of localized prostate cancer. At the same time, effort should be made to decrease the adverse effects of each treatment. Collaborative studies on the treatment of prostate cancer should be carried out among Asian countries.

Key words: prostate cancer – PSA screening – cancer prevention – isoflavone

INTRODUCTION
The topics discussed in this Prostate Cancer Working Group presentation are the incidence and mortality of prostate cancer in Asian countries, the current status of prostate-specific antigen (PSA) screening for prostate cancer in Asian countries, foods and substances for prevention of prostate cancer in Asian countries, and appropriate treatments for prostate cancer in Asians.

INCIDENCE AND MORTALITY OF PROSTATE CANCER IN ASIAN COUNTRIES
Historically, the incidence of clinically diagnosed prostate cancer in Asian countries has been lower than that in western countries. Recently, however, both the incidence and mortality rates of prostate cancer in Asian countries have been increasing. In spite of that, little research has been conducted to date among Asian populations.
Prostate cancer is the most common cancer among men in the USA. It is interesting to note that the incidence of prostate cancer in Japanese immigrants to Hawaii is higher than in Japanese living in Japan. This may be ascribed not only to genetic but also environmental factors. The incidence of prostate cancer in Japan has been increasing in recent years as Japanese adopt a more westernized lifestyle. This trend is expected to continue until at least 2020, because the younger generations of Japanese, who have a more westernized lifestyle, are aging. The annual trend in the age-adjusted incidence of prostate cancer in Korea is similar to that in Japan and has been increasing in recent years. Although both the incidence and ranking of prostate cancer are still low in comparison with western countries, its incidence and ranking among Korean male cancers is rising. The situation in Singapore is also similar, and prostate cancer now ranks as the third most common form of cancer among Singaporean men. Similar trends are seen in Indonesia and Malaysia, as well.

The mortality rate of prostate cancer has also been increasing in recent years, and it is projected to increase by 2.8 times in Japan by the year 2020. The Korean mortality rate due to prostate cancer mirrors the situation in Japan. In contrast to Asian countries, the prostate cancer mortality rate has started to decrease in the USA. This decrease is due to so-called ‘stage migration’, i.e. a decrease in the number of cases of advanced-stage cancer. This stage migration may be due to the very high rate of PSA screening in the USA. The 5-year survival rate for prostate cancer in the USA is extremely high, presumably due to early detection of the cancer. The total medical cost for prostate cancer is increasing, and that burden makes prostate cancer screening more difficult in developing Asian countries.

In conclusion, the incidence of prostate cancer is increasing rapidly in Asian countries due to a more westernized lifestyle. Prostate cancer mortality is declining in the USA, where most prostate cancers are diagnosed in the early stage. In contrast, the incidence and mortality rates of prostate cancer in Asian countries are expected to continue increasing, because the percentage of advanced-stage prostate cancers is still high. Therefore, early detection by PSA screening and a comprehensive strategy for cancer prevention are essential for Asian populations.

CURRENT STATUS OF PSA SCREENING FOR PROSTATE CANCER IN ASIAN COUNTRIES

The results of two randomized clinical studies of PSA screening have been published recently. One is the PLCO (prostate, lung, colorectal and ovarian) cancer screening study in the USA, and the other is the ERSPC (European Randomized Study of Screening for Prostate Cancer), which includes eight countries in Europe. These two studies address the controversy over the usefulness of PSA screening.

What do Asian countries think about PSA screening? In Japan, the Japanese Urological Association has issued a PSA screening guideline. Japanese urologists think that population-based PSA screening is useful and a screening system should be maintained. In the population-based PSA screening in Kanazawa City, the municipal government covers about 80% of the cost of the screening test. The number of candidates for screening is ~25,000 per year, and about 40 prostate cancer patients are diagnosed per year. The problem is the low exposure rate for the screening, which reaches only ~20% of the candidates. Of the total patients diagnosed with prostate cancer at Kanazawa University Hospital 4.3% had systemic symptoms at diagnosis, 22% had urological symptoms and 74% had high PSA levels in the screening, but no symptoms. The recurrence-free rate was higher for the PSA-screening patients than for the other patient groups (Fig. 1), and these results indicate that patients who are diagnosed without symptoms may have a better prognosis. It is very important to diagnose prostate cancer before manifestation of symptoms.

The rate of metastatic disease was compared between two cities in the Gunma prefecture with different PSA screening rates. The rate of metastatic disease decreased as the screening rate increased. A Japanese prospective cohort study was conducted in order to evaluate the effectiveness of screening. In Isesaki city, which is one of the model screening cities, the exposure rate to PSA screening was very high, 86%. Conversely, the exposure rate in the control cohort was very low, 13%, which may be the average exposure rate for PSA screening in Japan. Comparison of the age-related mortality rates due to prostate cancer in those two cohorts shows that the rate has decreased in Isesaki city since 2002, whereas the rate has increased in the control cohort. These are very preliminary data, and follow-up of the mortality rate in both the screening and control cohorts is necessary.

As in Japan, Korea has no national PSA-screening program. The Korean Urological Oncology Society conducted a population-based screening study. Screening regions were selected throughout Korea, and there were ~7,800 participants. In the study, 122 patients were diagnosed with prostate cancer, and the detection rate was ~3.3%. This detection rate in Korea is higher than that of other countries.

![Figure 1](i71.png) Recurrence free survival rates among three groups. Prostate-specific antigen (PSA) screening group was higher than that of other groups.
previously been reported in Japan and China. PSA screening may be useful for detection of prostate cancer in Korea. In Singapore, the official guidelines on health-screening state that men above 50 years old and having risk factors for prostate cancer should be screened. However, PSA screening has not spread, and patients are often diagnosed on the basis of abnormalities. There is thus a gap between policy and public perspective. Indonesia has no PSA screening system, and PSA is assayed in patients who display symptoms. In Malaysia, population screening is not recommended, and PSA is to be assayed in men with risk factors.

In conclusion, the exposure rate of PSA screening is very low in Asian countries. PSA screening may lower the mortality rate. The stances regarding population screening differ among countries. If population screening is to be spread, the urological associations should promote it. Finally, reliable data from Asian countries are needed.

**FOODS AND SUBSTANCES FOR PREVENTION OF PROSTATE CANCER IN ASIAN COUNTRIES**

The results of some observational studies are well known for showing that Asian countries have low rates of prostate cancer mortality and high rates of soy energy consumption (Table 1). The relative risk for prostate cancer was studied in relation to intake of genistein, which is an isoflavone. The higher the genistein dose, the lower the risk of prostate cancer became. The results of meta-analysis of case-controlled studies showed a statistically significant lower risk of prostate cancer, with an odds ratio of 0.74. Another meta-analysis focused on isoflavone consumption in association with the prostate cancer risk in men, and although the $P$ value was marginal, the odds ratio was 0.88.

In Korea, a number of unique agents have been thought to prevent prostate cancer. One of those is garlic, which is commonly used as a spice in Korea and contains organosulfur compounds and flavonoids. However, there is very little credible evidence of a relationship between garlic consumption and reduced prostate cancer risk. A second agent is soy, which has already been discussed above. Other agents include Vitamin E, selenium, tomatoes, carrots, oysters and so on, but the preventive effects of these agents have not been verified in controlled, randomized studies. Green tea is yet another candidate for the prevention of prostate cancer, but it was reported that there is insufficient evidence to give any firm recommendations regarding green tea consumption for cancer prevention.

In Indonesia, it has been thought that tofu, green tea and tomatoes are able to reduce prostate cancer, whereas in Malaysia the government has conducted an anti-smoking campaign to prevent many cancers, including prostate cancer. Singapore lists the same preventive factors.

In basic research, isoflavones have been shown to inhibit prostate cancer growth in nude mice (Fig. 2). Equol, an isoflavone, inhibited LNCaP cell growth in a dose-dependent manner. Some clinical trials have been conducted in Japan. One was a randomized, double-blind, placebo-controlled study that enrolled 89 participants who underwent prostate biopsy because of an elevated PSA level but had neither cancer nor prostatic intraepithelial neoplasia. The subjects were divided into two groups based on a PSA level of less than 10 or 10 or higher, and then each group was divided into two subgroups. One subgroup in each pair was administered placebo tablets, whereas the other took supplement tablets containing isoflavones and curcumin, an antioxidant. The patient randomization was well balanced. After 6 months of treatment, the PSA level was significantly reduced in the high baseline PSA subgroup that was administered the supplement compared with the high baseline PSA subgroup that was administered the placebo (Fig. 3). A second randomized clinical trial in Japan enrolled patients with benign prostatic hyperplasia, aged 50–75 years, with a PSA level of 2.5 or 3.0–10 ng/ml. A 6- to 12-core prostate

![Figure 2. Effects of isoflavones for the inhibition of prostate cancer growth in nude mice. Isoflavones have been shown to inhibit prostate cancer growth in nude mice.](image-url)
biopsy within the previous 12 months had been negative. The patients were randomized into a group and administered isoflavone 60 mg/day for 1 year or the placebo daily for 1 year, after which prostate biopsy was performed. The interim analysis of the results at 1 year from randomization showed that the isoflavone group had a relatively lower percentage of cancer-positive patients. Detailed analysis is ongoing.

In conclusion, the prostate cancer incidence is low in Asian countries, and one possible explanation is the high soy consumption. Isoflavones may prevent prostate cancer in Asian countries, but that is not yet clear. In the future, a large, multinational study in Asia is needed to clarify whether or not isoflavone consumption shows efficacy in preventing prostate cancer.

APPROPRIATE TREATMENTS FOR PROSTATE CANCER IN ASIANS

As described earlier, the incidence of prostate cancer is much lower in Asian countries than in Western countries. The incidence in Japanese–Americans in Hawaii is almost in the middle between Asia and the West. The mortality rate is also much lower in Asian–Americans than in other American racial groups. Several studies looked for genetic differences between Japanese and Caucasians. Some studies have reported a different hormonal environment among the races. Although the clinical practice guideline from NCI–PDQ for stage II prostate cancer does not include hormonal therapy in the treatment options, hormonal therapy is widely used in the USA as the initial treatment for prostate cancer according to the CaPSURE data.

The Working Group discussed the treatment trends in Asian countries. The data for Korea, Singapore and Indonesia show that hormonal therapy is widely used as the initial treatment, although the rates vary. In Japan, hormonal therapy is widely used for all stages of prostate cancer, not only for advanced stage disease. Data from the SEER program in the USA showed that Japanese patients with metastasis had a higher 5-year survival rate than Caucasians. Chinese showed a similar trend. These data suggest that hormonal therapy is more effective in Asians, because the patients in that study underwent hormonal treatment.

In consideration of the results of basic research, epidemiological studies and the trend of clinical practice in Japan, there is the question of whether hormonal therapy is more effective in Japanese patients. To address this issue, the clinical outcomes were compared between Japanese and Caucasian men after hormonal therapy for prostate cancer in Hawaii (1). The patient information was obtained from Queens Medical Center, the largest hospital in Hawaii. The patients’ clinical background characteristics were almost the same. The results revealed that the Japanese patients showed a much better prognosis than the Caucasians in terms of the overall survival rate (Fig. 4) and the cause-specific survival rate. The overall survival rate was also compared among Japanese, Caucasians, Chinese and Filipinos in Hawaii. The Chinese showed a trend that was similar to the Japanese.

Why did the Japanese patients show longer survival on hormonal therapy? Did they show greater sensitivity to the treatment? Did the treatment cause less toxicity? As noted earlier, it has been reported that Japanese have a different hormonal environment, including the CAG repeat frequency and 5α-reductase activity. Those research results are still controversial, but perhaps Japanese show greater sensitivity to hormonal treatment. Hormonal therapy has various adverse effects. In particular, cardiovascular disease and bone fractures increase the mortality rate. Several studies recently reported that androgen deprivation therapy (ADT)
increases cardiovascular disease and bone fractures, but the data are all from Western countries. It is important to know the side effects of hormonal therapy in Japanese and other Asian populations. Data for the general population show that the incidence of ischemic heart disease is much lower in Japanese than in Westerners. For bone fractures, as well, the incidence is much lower in Japanese than in Westerners. On the basis of those data, we can expect that the side effects of hormonal therapy will be less in Japanese and other Asian populations.

The J-CaP study was conducted by Professor Akaza as a kind of surveillance study of hormonal therapy in Japan. The data show that the cardiovascular mortality rate in Japanese patients undergoing ADT was almost the same as the rate in the general population, as had been expected. Also, we recently reported that osteoporosis due to ADT can be prevented by administration of risedronate, a bisphosphonate (2). Some of the ADT associated morbidities can be prevented by application of certain management strategies (Table 2), and a guideline for this is now being prepared. If the side effects of hormonal therapy can be prevented, this therapy would be even more effective for Asian populations. When localized prostate cancer patients were treated with primary androgen deprivation therapy (PADT), the overall survival curve was almost the same as the expected survival (Fig. 5) (3). This means that hormonal therapy is effective for localized prostate cancer, not just advanced prostate cancer. In Japan, a Clinical Practice Guideline for Prostate Cancer was published in 2006. On the basis of the results of some clinical trials, hormonal therapy for localized prostate cancer has been adopted as the recommendation grade B.

In conclusion, clinical guidelines should consider including hormonal therapy as one of the options for the treatment of localized prostate cancer. At the same time, effort should be made to decrease the adverse effects of each treatment. Collaborative studies on the treatment of prostate cancer should be carried out among Asian countries.

Conflicts of interest statement
None declared

Appendix
In addition to the authors listed in the author field, the following are the authors who contributed equally to this study.

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Table 2. Management strategies for ADT-associated morbidities

<table>
<thead>
<tr>
<th>Complication</th>
<th>Management strategy</th>
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<tbody>
<tr>
<td>Cardiovascular risk factors and disease</td>
<td>(i) Non-smoking</td>
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<td></td>
<td>(ii) Consultation for diet and exercise</td>
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<td></td>
<td>(iii) Regular monitoring of blood pressure</td>
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<tr>
<td>Osteoporosis and fractures</td>
<td>(i) Regular monitoring of BMD</td>
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<td>(ii) Consultation for exercise, diet with</td>
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<td>adequate calcium and Vitamin D intake</td>
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<td>(iii) Bisphosphonates</td>
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<td>Endocrine and metabolic dysfunction</td>
<td>(i) Consultation for nutrition, exercise and</td>
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<td>weight control prior to ADT</td>
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<td>(ii) Regular monitoring of HbA1c and fasting</td>
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<td>blood sugar</td>
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BMD, bone mineral density.
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